

General

Guideline Title

Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline.

Bibliographic Source(s)

Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, Stalenhoef AF. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012 Sep;97(9):2969-89. [191 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (+OOO, ++OO, +++O, and ++++); the strength of the recommendation (1 or 2); and the difference between a "recommendation" and a "suggestion" are provided at the end of the "Major Recommendations" field.

Diagnosis and Definitions

Severe and very severe hypertriglyceridemia increase the risk for pancreatitis, whereas mild or moderate hypertriglyceridemia may be a risk factor for cardiovascular disease. Therefore, similar to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guideline committee's recommendations, the Task Force recommends screening adults for hypertriglyceridemia as part of a lipid panel at least every five years (1|++OO).

The Task Force recommends basing the diagnosis of hypertriglyceridemia on fasting triglyceride levels and not on nonfasting triglyceride levels (1|+++O).

The Task Force recommends against the routine measurement of lipoprotein particle heterogeneity in patients with hypertriglyceridemia (1|++OO). The Task Force suggests that measurement of apolipoprotein B (apoB) or lipoprotein(a) [Lp(a)] levels can be of value, whereas measurement of other apolipoprotein levels has little clinical value (2|++OO).

Causes of Elevated Triglycerides—Primary and Secondary

The Task Force recommends that individuals found to have any elevation of fasting triglycerides should be evaluated for secondary causes of hyperlipidemia including endocrine conditions and medications. Treatment should be focused on such secondary causes (1|++OO).

The Task Force recommends that patients with primary hypertriglyceridemia be assessed for other cardiovascular risk factors, such as central

obesity, hypertension, abnormalities of glucose metabolism, and liver dysfunction (1|++OO).

The Task Force recommends that clinicians evaluate patients with primary hypertriglyceridemia for family history of dyslipidemia and cardiovascular disease to assess genetic causes and future cardiovascular risk (1|++OO).

Management of Hypertriglyceridemia

The Task Force recommends lifestyle therapy, including dietary counseling to achieve appropriate diet composition, physical activity, and a program to achieve weight reduction in overweight and obese individuals as the initial treatment of mild-to-moderate hypertriglyceridemia (1|++OO).

For severe and very severe hypertriglyceridemia (>1000 mg/dl), the Task Force recommends combining reduction of dietary fat and simple carbohydrate intake with drug treatment to reduce the risk of pancreatitis (1|++++).

The Task Force recommends that the treatment goal for patients with moderate hypertriglyceridemia be a non-high-density lipoprotein (HDL) cholesterol level in agreement with NCEP ATP guidelines (1|++OO).

The Task Force recommends that a fibrate be used as a first-line agent for reduction of triglycerides in patients at risk for triglyceride-induced pancreatitis (1|+++O).

The Task Force suggests that three drug classes (fibrates, niacin, n-3 fatty acids) alone or in combination with statins be considered as treatment options in patients with moderate to severe triglyceride levels (2|++OO).

The Task Force recommends that statins not be used as monotherapy for severe or very severe hypertriglyceridemia. However, statins may be useful for the treatment of moderate hypertriglyceridemia when indicated to modify cardiovascular risk (1|++OO).

Definitions:

Quality of the Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Strength of Recommendations

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Hypertriglyceridemia

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Screening

Treatment

Clinical Specialty

Cardiology

Endocrinology

Family Practice

Internal Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To develop clinical practice guidelines on hypertriglyceridemia

Target Population

Adults

Interventions and Practices Considered

Screening/Evaluation

1. Screening adults as part of lipid panel at least every 5 years
2. Diagnosis based on fasting triglyceride levels
3. Measurement of apolipoprotein B (apoB) or lipoprotein(a) [Lp(a)]
4. Evaluation for secondary causes of hyperlipidemia, including endocrine conditions and medications
5. Assessment for other cardiovascular risk factors, including obesity, hypertension, and liver dysfunction
6. Evaluation of family history to assess genetic causes and future cardiovascular risk

Treatment/Management

1. Lifestyle therapy, including dietary counseling, physical activity, and weight reduction program
2. Drug treatment with reduction of fat and carbohydrate intake for those at risk for pancreatitis
3. Treatment goal of non-high-density lipoprotein (HDL) cholesterol levels consistent with National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) guidelines
4. Fibrates for those at risk for triglyceride-induced pancreatitis

5. Fibrates, niacin, n-3 fatty acids alone or in combination with a statin

Major Outcomes Considered

- Cardiovascular or total mortality
- Cardiovascular events
- Pancreatitis
- Sensitivity and specificity of serum triglyceride testing
- Treatment effectiveness (lifestyle and/or pharmacological) in modifying cardiovascular disease risk

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Study Identification and Data Extraction

An expert reference librarian created and implemented the electronic search strategy with input from study investigators. Ovid MEDLINE, Ovid EMBASE, Web of Science and SCOPUS through August of 2010 were searched. The detailed search strategy is available in the systematic review (see the "Availability of Companion Documents" field). Recommendations were sought from content expert for potentially relevant studies to be included in the screening process.

Reviewers working independently and in duplicate assessed each abstract for eligibility. Disagreements yielded an automatic inclusion into the following level of screening. Included studies were retrieved and full text screening commenced in duplicate as well. Disagreements in this level were resolved by discussion and consensus. Online reference management system was used to conduct this review and it reported a real-time chance-adjusted agreement (kappa) statistic to evaluate the agreement among reviewers. Kappa averaged 0.80. Two reviewers working independently and in duplicate extracted baseline and outcome data and assessed the quality of the included study. A third reviewer compared the reviewers' data and resolved inconsistencies by referring to the full text article.

Eligibility Criteria

Eligible studies were randomized and observational studies that enrolled patients with untreated hypertriglyceridemia and reported a relative association measure between fasting and/or nonfasting serum triglycerides levels and the outcomes of interest: all cause mortality, cardiovascular death, cardiovascular events and pancreatitis. Uncontrolled studies were excluded.

Number of Source Documents

The electronic search yielded 760 potentially eligible studies. Following screening, 60 studies met inclusion criteria, of which 40 reported data sufficient for meta-analysis.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of the Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

Methods Used to Analyze the Evidence

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Quality

Using the Newcastle-Ottawa scale, reviewers assessed the quality of included observational studies (and control arms of randomized control trials [RCT], considered as observational cohorts) by determining outcome ascertainment, adjustment for confounders, proportion of patients lost to follow-up as well as sample selection. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used in evaluating the evidence yielded from included studies.

Statistical Analysis

The Task Force pooled the relative association measures of relevant complications from included studies and analyzed the data using the random-effects model described by DerSimonian and Laird. Heterogeneity in results across studies was measured using the I^2 statistic, which estimates the proportion of variation in results across studies that is not due to chance. An I^2 of 50% or more indicates large inconsistency between studies. Meta-analysis was completed using Comprehensive Meta-analysis (CMA) version 2.2 (Biostat Inc., Englewood, NJ).

Subgroup Analyses and Publication Bias

A priori hypotheses were designed to explain between-study inconsistencies in results: the analyses sought an interaction with fasting vs non-fasting triglycerides levels and whether triglycerides levels were adjusted for other lipid fractions or not. Publication bias was evaluated by assessing the symmetry of funnel plots and using Egger's regression test to detect asymmetry of the plot. In the regression, the size of the treatment effect is captured by the slope of the regression line and is captured by the intercept.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Participants

The Task Force included a chair selected by The Endocrine Society Clinical Guidelines Subcommittee (CGS), five additional experts in the field, and a methodologist.

Evidence

The Task Force followed the approach recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) group. A detailed description of this grading scheme has been published (see the "Rating Scheme for the Strength of the Evidence" and the "Rating

Scheme for the Strength of the Recommendations" fields). The quality of the evidence indicates the panel's confidence that the estimates of risks and benefits associated with the recommended course of action compared with an alternative course of action are correct and unlikely to change importantly with new research.

Consensus Process

Consensus was guided by systematic reviews of evidence, e-mail discussion, conference calls, and one in-person meeting.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Cost Analysis

A cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

The guidelines were reviewed and approved sequentially by The Endocrine Society's Clinical Guidelines Subcommittee (CGS) and Clinical Affairs Core Committee, members responding to a web posting, and The Endocrine Society Council. At each stage, the Task Force incorporated changes in response to written comments.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is specifically stated for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Improved diagnosis, evaluation, and management of hypertriglyceridemia

Potential Harms

- The use of niacin is associated with significant side effects. The most common side effect of niacin is cutaneous flushing, which is most significant with the first few doses. The most serious complication of niacin therapy is hepatotoxicity (which is dose dependent), and therapy should be accompanied by monitoring of liver function tests. Other side effects of niacin therapy include impairment or worsening of glucose tolerance and hyperuricemia. Niacin could cause conversion of borderline glucose intolerance to meet diabetes criteria in some patients. Niacin can increase blood levels of uric acid by blocking its excretion and can precipitate or worsen gout unless the patient is treated with

allopurinol.

- Fibrate side effects include gastrointestinal discomfort and possibly an increased incidence of cholesterol gallstones. Fibric acid derivatives should be used with great caution in the setting of renal insufficiency because the drugs are excreted in the urine and may reversibly increase serum creatinine levels—especially fenofibrate, although the significance of this effect is unknown. Due to effects on protein binding, there is a potential interaction with warfarin requiring careful monitoring.
- Side effects with large doses of omega-3 fatty acids include fishy taste and burping.
- Side effects of statins occur in about 5%–10% of patients. Muscle symptoms ranging from leg cramps to aching to weakness occur in about 10% of patients, whereas rhabdomyolysis is rare. Conditions predisposing to severe myopathy include advanced age, renal failure, polypharmacy, and acute illness.
- With combination drug treatment, attention needs to be paid to potential drug-drug interaction.

Contraindications

Contraindications

- Fibrates are contraindicated in patients with liver and gall bladder disease.
- Niacin is contraindicated in patients with active peptic ulcer disease.

Qualifying Statements

Qualifying Statements

- Clinical Practice Guidelines are developed to be of assistance to endocrinologists and other health care professionals by providing guidance and recommendations for particular areas of practice. The Guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances.
- The Endocrine Society makes no warranty, express or implied, regarding the Guidelines and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The Society shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein.
- In developing the recommendations for the management of hypertriglyceridemia, the Task Force acknowledges the observational nature of the available evidence and the dependence on epidemiological studies.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: This guideline was not adapted from another source.

Date Released

2012 Sep

Guideline Developer(s)

The Endocrine Society - Professional Association

Source(s) of Funding

Funding for this guideline was derived solely from The Endocrine Society.

Guideline Committee

Hypertriglyceridemia Task Force

Composition of Group That Authored the Guideline

Task Force Members: Lars Berglund (*Chair*), John D. Brunzell, Anne C. Goldberg, Ira J. Goldberg, Frank Sacks, Mohammad Hassan Murad, and Anton F. H. Stalenhoef

Financial Disclosures/Conflicts of Interest

Lars Berglund, M.D., Ph.D. (*Chair*)—Financial or Business/Organizational Interests: NIH, AHA, Pfizer, Astra-Zeneca, Danone; Significant Financial Interest or Leadership Position: AHA, Pfizer, AstraZeneca.

John D. Brunzell, M.D.—Financial or Business/Organizational Interests: American Diabetes Association, Endocrine Society, Amsterdam Molecular Therapeutics, Lexicon Genetics, Merck Research Laboratories, Daiichi Sankyo, University of Washington; Significant Financial Interest or Leadership Position: none declared.

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Mohammad Hassan Murad, M.D.*—Financial or Business/Organizational Interests: KER Unit (Mayo Clinic); Significant Financial Interest or Leadership Position: none declared.

Anton F. H. Stalenhoef, M.D., Ph.D., F.R.C.P.—Financial or Business/Organizational Interests: Dutch Heart Foundation, Merck, Genzyme, Roche; Significant Financial Interest or Leadership Position: Dutch Journal of Medicine, Current Opinion Lipidology.

*Evidence-based reviews for this guideline were prepared under contract with The Endocrine Society.

Guideline Endorser(s)

American Heart Association - Professional Association

European Society of Endocrinology - Medical Specialty Society

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from [The Endocrine Society Web site](#) .

Print copies: Available from The Endocrine Society, Phone: (301) 941.0210; Email: Societyservices@endo-society.org

Availability of Companion Documents

The following is available:

- Murad MH, Hazem A, Coto-Yglesias F, Dzyubak S, Gupta S, Bancos I, Lane M, Erwin PJ, Berglund L, Elraiyah TB, Montori VM. The association of hypertriglyceridemia with cardiovascular events and pancreatitis: A systematic review and meta-analysis. BMC Endocrine Disorders. 2012 Mar 31;12:2. Electronic copies: Available in Portable Document Format (PDF) from the [BioMed Central Web site](#) .

Print copies: Available from The Endocrine Society, Phone: (301) 941.0210; Email: Societyservices@endo-society.org

Patient Resources

The following is available:

- Patient guide to the assessment and treatment of hypertriglyceridemia (high triglycerides). The Hormone Foundation. 2012 Sep. 2 p. Electronic copies: Available from [The Hormone Foundation Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on November 1, 2012. The information was verified by the guideline developer on December 3, 2012.

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